REMARKS

This Application has been amended in a manner it is believed to place it in condition for allowance at the time of the next Official Action.

Claims 1-20 are pending in the application.

Claims 1-2 and 5-14 remain unchanged.

Claims 3, 4, 8, and 13-14 have been amended to address formal matters.

New claims 15-20 to vary the scope of the claimed invention. Support for the new claims may be found generally throughout the specification and in the original claims. In particular, support for the new claims may be found in the present specification at page 3, lines 1-22 and at page 2, lines 9-17.

Applicants submit that no new matter has been added to the disclosure.

Claims 3 and 4 were objected to for allegedly containing several informalities.

As noted above, Applicants have amended claims 3 and 4 to address these informalities. The acronyms PEG and PLGA have been identified with their proper terminology. Applicants respectfully request that the objections be withdrawn.

The specification was objected to for improperly referring to a trademark. This objection is traversed.

The specification has been amended to indicate that LIPIODOL™ is a registered trademark. In this regard, Applicants submit herewith a clean version of the specification and a marked-up version of the specification to indicate the changes that have been made. Applicants respectfully request that no new matter

has been added.

Claims 1-14 were rejected under 35 U.S.C. 103(a) for allegedly being unpatentable over SAWHNEY (U.S. Patent No. 6,632,457) and further in view of JEONG et al. (Marcomolecules, Vol. 33, 2000, pp. 8317-8322). This rejection is traversed.

SAWHNEY discloses a composite hydrogel drug delivery system. The Examiner's attention is respectfully directed to Example 1, Figure 1, and Figure 2 of SAWHNEY. The composite hydrogel drug delivery system is a microsphere SAWHNEY teaches that the microspheres are capable of controlling the release rate of the therapeutic agent. In general, the microspheres are degraded during the process as follows: (1) swelling with water, (2) drug diffusion through water channel, and (3) drug release from matrix erosion. Thus, the microspheres have been designed to swell and diffuse a drug through a water channel and matrix erosion.

The microspheres of SAWHNEY are <u>not</u> a temperature-sensitive thermogelling emulsion delivery system (i.e. thermal-sensitive in situ forming hydrogel matrix). For example, Poloxamer 407 may serve as drug delivery system due to slow dissolution of polymer into the aqueous surroundings, but itself is not a biodegradable polymer.

In imposing the rejection, the Official Action cites to column 8, line 16 of SHAWHNEY for the proposition that SAWHNEY teaches "embedding" a bioactive substance with an oil phase carrier. However, the passage at column 8, lines 1-30 suggests that this occurs within a "hydrophobic domain" of the microparticle.

SAWHNEY does not teach "embedding" a bioactive substance with an oil phase carrier within temperature-sensitive thermogelling emulsion delivery system. Moreover, there is no recognition of temperature-sensitive thermogelling emulsion delivery system having an oil carrier embedding a bioactive substance in a soluble in oil, solid-in-oil, or water-in-oil form as recited in claims 8, 15, and 19.

Furthermore, the release mechanism of the microspheres stands in contrast to that of a thermal-sensitive *in situ* forming hydrogel matrix (matrix) of the present invention. The matrix typically contains more than 60% of water and does not go through a step of swelling. As noted on page 2 of the present specification, polymers used for hydrogel applications have been developed. However, while hydrogels can safely encapsulate drugs without resorting to extreme conditions, these hydrogels have a high water content. As a result, hydrophilic molecules diffuse out easily through water-rich channels and most of the drugs are released rapidly in the early stage after the injection. This is referred to as the 'burst release'.

In view of the distinct structure and release mechanism utilized by the SAWNHNEY microspheres, Applicants respectfully submit that one skilled in the art would lack the motivation to combine and modify the SAWNHNEY microspheres with other drug delivery systems when looking for a new way to deliver a drug having a distinct release mechanism, especially a temperature-sensitive thermogelling delivery system as claimed. For example, Poloxamer 407 may serve as drug delivery system due to slow dissolution of polymer into the aqueous surroundings,

but itself is not a biodegradable polymer.

Nevertheless, in an effort to remedy the deficiencies of SAWHNEY for reference purposes, the Official Action cites to JEONG.

JEONG (Macromolecules, vol. 33, 2000, pp. 8317-22; D2) discloses copolymers that are thermal-sensitive *in situ* hydrogels. JEONG does not disclose or suggest a temperature-sensitive thermogelling emulsion delivery system as claimed. In this regard, JEONG fails to remedy the deficiencies of SAWHNEY for reference purposes.

Indeed, as noted in the last paragraph of the Introduction, these copolymers can be used in a short-term delivery system. In this regard, even if one skilled in the art applied the copolymers of JEONG with the SAWHNEY microspheres, one skilled in the art would at best produce microspheres having copolymers. Neither publication discloses nor suggests modifying microspheres to obtain a temperature-sensitive thermogelling emulsion delivery system.

In KSR v. Teleflex, 550 U.S. 398 (2007), the Supreme Court noted that an invention may have been obvious"[w]hen there [was]. . . a design need to market pressure to solve a problem and there [were] . . . a finite number of identified, predictable solutions." 127 S. Ct. at 1742 (tense changes supplied to clarify, as the Court sated and as per 35 U.S.C. § 103, that the obviousness inquiry must rely upon evidence available "at the time" of the invention, see Takeda, 492 F.3d at 1356 n.2).

The Supreme Court's analysis in KSR assumes a starting reference point or points in the art, prior to the time of invention, from which a skilled artisan might identify a

problem or pursue potential solutions.

Second, KSR presupposes that the record up to the time of invention would give some reasons, available within the knowledge of one of skill in the art, to make particular modifications to achieve the claimed compound. See Takeda, 492 F.3d at 1357 ("Thus, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound.").

Third, the Supreme Court's analysis in KSR presumes that the record before the time of invention would supply some reasons for narrowing the prior art universe to a "finite number of identified, predictable solutions," 127 S. Ct. at 1742. In Ortho-McNeil Pharmaceutical, Inc., v. Mylan Laboratories, Inc., 520 F.3d 1358, 1364 (Fed. Cr. 2008), the Federal Circuit further explained that this is "easily traversed, small and finite number of alternatives . . . might support an inference of obviousness." To the extent an art is unpredictable, as the chemical arts often are, KSR's focus on these "identified, predictable solutions" may present a difficult hurdle because potential solutions are less likely to be genuinely predictable.

In view of the above, the release profile and combination of thermal sensitive *in situ* forming emulsion can not be predicted by either preformed microspheres or general *in situ* forming hydrogels as suggested by the Official Action. In light of this unpredictability, it can not be said that any of the pending claims are predictable.

Furthermore, if these copolymers are used for drug delivery, the burst effect

would likely proceed in an uncontrolled manner as described on page 3 and shown in the release profile of Example 9 of the present invention. Indeed, the emulsion of the present invention has an unexpected and unique property (i.e., long-term sustained release) as compared to a hydrogel matrix relating (e.g., see Example 10 of the present invention). Thus, in view of the above, Applicants respectfully request that the rejection be withdrawn.

The Examiner is respectfully reminded that the Patent Office must consider objective indicia of nonobviousness whenever present. Specifically, the Patent Office is bound to consider evidence of unexpected results, commercial success, long-felt but unresolved needs, failure of others, skepticism of experts. Stratoflex, Inc. v. Aeroquip Corp., 713 f. 2d 1530, 1538 (Fed Cir. 1983). Federal Circuit precedent mandates consideration of comparative data in the specification which is intended to illustrated the claimed invention in reaching a conclusion with regard to the obviousness of the claims. In re Margolis, 785 F. 2d 1029 (Fed Cir. 1986). (Vacating Board decision which refused to consider data in the specification which compared an embodiment of the invention with the prior art product and noting that such evidence spoke to unexpected results and non-obviousness).

In view of the unexpected and unique properties exhibited by the claimed invention, Applicants respectfully submit that the proposed combination fails to render obvious any of the claims.

In view of the above, Applicants respectfully request that the obviousness rejection be withdrawn.

Applicants respectfully submit that the present application is in condition for allowance at the time of the next Official Action. Allowance and passage on that basis is respectfully requested.

Respectfully submitted,
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APPENDIX

- Marked-up version of the specification.
- Clean version of the specification.